Please replace the paragraph starting at page 8, line 18, with the following:

By screening combinatorial peptide libraries, we identified two peptide ligands for CTL expressing the prevalent Vα17-MRD-Jα42 TCRα chain: NRP (KYNKANWFL) and NRP-A7 (KYNKANAFL), an alanine mutant analog of NRP with superior agonistic properties (37). These two peptides elicit the proliferation, cytokine secretion, differentiation and cytotoxicity of naive $CD8^+$ T-cells from 8.3-TCRαβ-transgenic NOD mice, and are recognized by a large fraction of the islet-associated $CD8^+$ T-cell lines (87%) and clones (45%) recruited to islets in NOD mice. This observation has thus provided additional support to our view that activation of the $CD8^+$ T-cells that contribute to the progression of spontaneous IDDM is triggered by recognition of a few peptide/MHC class I complexes on beta cells or islet-associated APCs (37). It is important to point out, however, that this does not imply that the $CD8^+$ T-cell response in autoimmune diabetes is exclusively directed against one peptide. Wong et al., for example, have reported that insulitic $CD8^+$ T-cells in young NOD mice recognize an insulin-derived peptide (38). In our hands, however, these cells represent a very small fraction of all islet-derived $CD8^+$ T-cells, particularly in mice older than 6 weeks (see below and reference 39).

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Please replace the paragraph starting at page 13, line 10, with the following:

Figure 7 presents the NRP-reactivity of islet-associated $CD8^+$ T cells from NOD mice (37). As shown in Fig. 7A, most $CD8^+$ T cells propagated from islets of acutely diabetic NOD mice (7 of 8 -87.5%-, Fig. 7C) killed NRP- (but not negative control peptide (TUM))-pulsed RMA-SKd cells *in vitro*. Of 31 $CD8^+$ CTL clones generated from islets of 9 NOD mice which were tested, 14 (45%) were cytotoxic against NRP-, but not TUM-pulsed, RMA-SKd targets (Fig. 7B and C).

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Please replace the paragraph starting at page 21, line 12, with the following:

To test the validity of this hypothesis, we produced mimics of NRP capable of engaging the 8.3-TCR (a TCR that is representative of the TCRs used by NRP-reactive $CD8^+$ T cells in the NOD mouse) with very low or very high affinity (when compared to

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NRP and NRP-A7). This was done by generating numerous single amino acid mutants of NRP (NRP mimics) and by testing the ability of each mutant to elicit proliferation, cytokine secretion and cytotoxicity of naïve or activated 8.3-CD8$^+$ T cells. The results of these experiments are summarized in Figure 13. Some of the NRP mimics that were unable to elicit the activation of naïve 8.3-CD8$^+$ T cells were tested for antagonism. Antagonist mimics are unable to elicit the functional activity of T cells but antagonized the agonistic activity of functional mimics (i.e. NRP and NRP-A7). These experiments resulted in the identification of two NRP antagonists: NRP-A4 and NRP-A8 (Fig. 14). Of these, NRP-A4 (SEQ ID NO:3) was the most powerful and was chosen for further experimentation. Partial agonists and super/super-agonists were chosen among NRP mimics capable of triggering 8.3-CD8$^+$ T cell activation (Fig. 13). NRP-I4 (SEQ ID NO:4) behaved as a partial agonist since it could only trigger IFN-gamma secretion by naïve 8.3-CD8$^+$ T cells. NRP-V7 (SEQ ID NO:5) was chosen as a super/super-agonist since it had superior agonistic activity when compared to NRP (agonist) and NRP-A7 (super-agonist). Fig. 15 compares the agonistic properties of all these peptides on naïve 8.3-CD8$^+$ T cells.

Please replace the paragraph starting at page 25, line 9, with the following:

Thus, both low and high doses of each of TUM (negative control; SEQ ID NO:6), NRP-A4 (low avidity), NRP-I4 (moderate avidity), NRP (intermediate avidity), NRP-A7 (high avidity) and NRP-V7 (very high avidity) were given to NOD mice and the effects were assessed (Example 11). The results (Table II) indicate that low dosage of NRP-A4 had no effect, while a high dose was anti-diabetogenic. NRP-I4 accelerated diabetes at a low dose but protected the mice from diabetes at a high dose. NRP-A7 was anti-diabetogenic at low dosage, and had no effect at high dosage. NRP-V7 was ineffective on the diabetic incidence at either low or high dosages.

Please replace the paragraph starting at page 32, line 25, with the following:

In order to follow the accumulation of antigen-specific CD8$^+$ T cells in islets of pre-diabetic NOD mice, we generated H-2Kd tetramers containing the peptides NRP, NRP-A7,

TUM or INS (LYLVCGERG (SEQ ID NO:7); an insulin-derived peptide recognized by islet-associated T cells from young NOD mice (38)). The NRP and NRP-A7 tetramers stained virtually all the splenic $CD8^+$ T cells from 8.3-TCR$\alpha\beta$-transgenic NOD mice, but $<1\%$ of the splenic $CD8^+$ T cells from NOD mice. The INS tetramer stained the INS-reactive CTL clone G9C8 (38), but neither this tetramer nor the negative control tetramer (TUM) stained the splenic $CD8^+$ T cells from NOD or 8.3-TCR$\alpha\beta$-transgenic NOD mice (data not shown).

Please replace the paragraph starting at page 33, line 5, with the following:

Since tetramer-reactive cells represent a very small fraction of all the islet-associated T cells, we analyzed the presence of tetramer-reactive clonotypes within the cell population that has undergone antigen-driven activation and thus is likely to contain autoreactive specificities. Islets from non-diabetic 5, 9, 15 and 20 wk-old NOD mice were cultured in the presence of rIL-2 for 6-7 d, to selectively expand IL-2R-positive T cells ($\sim 10\%$ of all the islet-associated $CD8^+$ T cells (30)). There were age-dependent increases in the number of T cells recovered from NOD islets and in the % of $CD8^+$ T cells contained within lines. Tetramer staining indicated that NRP/NRP-A7-reactive $CD8^+$ T cells constitute a significant fraction of the *in vivo*-activated $CD8^+$ T cells contained within islets (Figs. 8A, B). Notably, the size of the NRP-A7-reactive $CD8^+$ T cell population increased with age, reaching $\sim 18\%$ by 15 wk (Figs. 8A, B). This increase was antigen-specific, since the number of NRP/NRP-A7-reactive $CD8^+$ T cells was significantly greater than the number of INS (and TUM)-reactive $CD8^+$ T cells at all ages tested, except 5 weeks (Figs. 8A, B). Surprisingly, the number of NRP-A7-reactive $CD8^+$ T cells at 20 wk was significantly greater than the number of NRP-reactive $CD8^+$ T cells (Figs. 8A, B). This was not an artifact of *in vitro* culture since pancreatic lymph node cells from 20 wk-old, but not 3-5 wk-old NOD mice bind the NRP-A7 tetramer more efficiently than the NRP tetramer (Fig. 9). Since most, if not all the NRP-reactive lines are also NRP-A7-reactive, but not *vice versa* (Fig. 8C), and since at least one of the Vα17-MRD-Jα42-expressing T cell clones isolated by DiLorenzo et al. (36) recognizes NRP-A7 but not NRP (Fig. 10), the above

data suggested that the age-dependent increase in the size of the NRP/NRP-A7-reactive population is accompanied by an outgrowth of clones capable of recognizing NRP-A7 but not NRP. Furthermore, since NRP/NRP-A7-reactive clonotypes (i.e. 8.3-CTL) bind the NRP-A7 tetramer with longer half-life and higher avidity (lower K_D) than the NRP tetramer (Figs. 11A and 11B), we reasoned that the outgrowing clonotypes might be those with the highest avidity for NRP-A7/H-2Kd binding.